



NAVY DEPARTMENT

## BUMED NEWS LETTER

a digest of timely information

Editor - Captain F. W. Farrar. (MC). U.S.N.

*Notice: Items marked "Restricted" should not be published or communicated to any one except for official purposes.*

Vol. 10

Friday, 1 August 1947

No. 3

TABLE OF CONTENTS

Prognosis in Lower-Bowel Cancer....2	Experimental Renal Calculus .....23
Lower-Bowel Precancerous Lesions..6	Neuromuscular System & Arthritis..25
The Stevens-Johnson Syndrome .....9	Activation of DC Volunteer USNR...27
Toward Order from Rh Chaos.....11	Training of Technicians, DC, USNR.27
Study of Commercial Rh Antiserums.17	Training in Preventive Medicine....27
Autohemagglutinins & Raynaud's ....19	Research and Special Assignments ..28
Composition of Urinary Calculi.....21	Medical Material Catalog Changes .28
Public Health Foreign Reports.....30	

Circular Letters:

Resignations of NC Officers: Method of Submission .....	BuMed.....	31
Re Precious Metal Expenditures Listed on Dental Reports.....	BuMed.....	31
Tuberculin-Testing of Navy and Marine Corps Personnel .....	BuMed.....	31
Dental Activities' Financial and Property Accountability .....	BuMed.....	32

\* \* \* \* \*

\* \* \*

\*

(Not Restricted)

Prognosis in Carcinoma of the Colon and Rectum: It is a well known but occasionally forgotten fact that the term "five-year cure" is little more than a convenient yardstick when used in connection with patients suffering from cancer. It will give an approximate idea of the end-results in a group of patients with cancer in one site or another, but it cannot be applied to the individual patient because some of those persons who survive for five years following the removal of their cancer will ultimately die of a recurrence. This is true of carcinoma of the colon and rectum just as it is of carcinoma of other viscera and the breast. It is of interest and of value to know the results in patients with carcinoma of the colon and rectum five years after operation and what the chances are for an individual patient to live, not only five years, but 10 or more years following resection of the malignant tumor.

The spread of carcinoma of the colon or rectum through the adjacent lymphatics has long been understood. For many years the author and co-workers have routinely isolated and examined the mesenteric lymph nodes in each resected specimen for the presence of metastatic carcinoma. The significance of lymph-node involvement in the prognosis for the individual patient is apparent from the present study and from the cases reported in the literature. Only in recent years, however, has the frequency with which carcinoma of the colon and rectum may spread through the vascular system been fully appreciated. Any discussion of prognosis following resection for carcinoma of the colon and rectum should emphasize the seriousness of blood vessel invasion as seen in the microscopic examination of the resected specimen. In one study of 208 patients the author and co-workers found that, of those patients who had shown blood vessel invasion at the time of operation, only 15 per cent were alive five years later.

In the present study, the case histories of 337 patients with carcinoma of the colon and rectum were carefully reviewed. All of these patients were first seen prior to 1936.

The patients were divided into two main groups. In the first group were those with carcinoma of the colon, including carcinoma of the cecum, ascending, transverse, descending, and upper sigmoid colon. The second group consisted of patients with carcinoma of the lower sigmoid, rectosigmoid, and rectum, since in these cases some type of resection of the rectum and rectosigmoid, with the establishment of a proximal colostomy, was carried out.

There were 103 patients with carcinoma of the colon. The youngest patient was 27 years of age, the oldest 74, and the average age was 57 years. The incidence of carcinoma of the colon was slightly higher in women (56) than in men (47), whereas the reverse was true for carcinoma of the rectum.

(Not Restricted)

Eighty-one of the 103 patients were submitted to some type of resection, including 14 palliative resections. This is a resectability or operability rate of 78.6 per cent. Three of the resections were palliative because of the presence of liver metastases at the time of operation; and 11 others were considered so because of local invasion found at the time of resection. There were 22 patients in whom resection was not considered feasible. Three patients were not operated on, 4 had laparotomy only, 2 had cecostomy, and 13 had a side-tracking anastomosis, such as an ileotransverse colostomy or colocolostomy.

Five deaths occurred in the group of patients in whom the malignant tumor was limited to the bowel wall. Eight deaths occurred in the group in which the carcinoma already had invaded either the adjacent lymph nodes or neighboring viscera. This is a mortality rate of 16.0 per cent in the resected cases. In line with the marked reduction of the mortality noticed in all surgical centers interested in the treatment of carcinoma of the colon, the mortality rate in patients of this type in 1945 was 2.3 per cent. This lowered mortality rate was accomplished in spite of the fact that the operability rate has continued to rise and in 1945 was 90.7 per cent. Three deaths occurred among those patients in whom only laparotomy or a palliative anastomosis was possible.

In the group in which the regional lymph nodes and adjacent viscera were not involved there were 38 patients in whom the 10-year follow-up was complete. Of this group, 5 patients died in the hospital; 5 other patients subsequently died from causes other than recurrences of the carcinoma. These patients had lived from 3 months to 8 years following operation with no evidence of recurrence at the time of death from other causes. Of the remaining 28 patients, 18 were living and well at the end of 5 years, 2 died of recurrent malignant disease between their fifth and tenth postoperative years, and 16 were living and well 10 or more years following resection of their malignant lesion. In 12 additional cases the 10-year follow-up was incomplete, although 6 of these 12 patients are known to have been living and well 5 or more years after operation. Thus, in the group of patients who survived operation and in whom the 10-year follow-up was complete, the 5-year survival rate was 64.3 per cent and the 10-year survival rate 57.1 per cent.

Of the 27 patients in whom the malignant disease had extended to the adjacent lymph nodes or involved the surrounding structures, 8 died in the hospital and 15 died of recurrence of their disease within 5 years. One patient died of a recurrent carcinoma after having survived 5 years, and 3 patients are living and well 10 or more years after operation. Thus, for this initially unfavorable group, the survival rate dropped to 14.8 per cent 5 years after operation and to 11.1 per cent 10 years after operation. One patient with

(Not Restricted)

sarcoma of the colon died less than 18 months after operation from recurrence of his malignant disease. Four patients in whom resection was done in the presence of liver metastases lived from 1 to 5 years following operation. In the one case in which the patient survived more than 3 years, there is some question of whether the nodules noted in the liver at the time of operation were actually metastases, since no biopsy specimen was obtained. Of the 4 cases in which laparotomy only was performed, not 1 patient survived a year. The same was true for the 13 patients in whom only a side-tracking anastomosis was carried out.

There were 234 patients with carcinoma of the rectum and rectosigmoid. Of these, 129 were males and 105 were females. Their ages ranged from 21 to 75 years, with an average age of 57 years. It is worth while to note again that carcinoma of the rectum is found not uncommonly in patients below the so-called "cancer age." Nineteen patients, or 8 per cent of the entire group, were under 40 years of age.

One hundred forty-six patients (62 per cent) of this group had some type of resection. A two-stage Lahey procedure was performed in 83 or 56.8 per cent of the 146 patients, a one-stage abdominoperineal (Miles) resection in 24, or 16.4 per cent, a posterior resection in 22, or 15.0 per cent, and an anterior resection (with permanent colostomy) in 17, or 11.6 per cent. Eighteen of these resections were considered palliative, 11 definitely so because of the presence of liver metastases and 7 probably so because of invasion of adjacent structures. A steady tendency toward the increasing use of the one-stage Miles abdominoperineal resection is shown by the fact that this procedure was used in 16.4 per cent of the above group, in 76.7 per cent in the year 1941, and 97.5 per cent in 1945. Resection was not carried out in 88 cases, a colostomy having been done in 62, a first-stage Lahey procedure in 10, and a laparotomy only in 11. No operation was performed in 5 cases.

Of the 146 patients who were submitted to resection, including 18 palliative resections, there were 11 deaths, or a mortality for the resected cases of 7.5 per cent. Since 1936 the operative mortality for carcinoma of the rectum has dropped to 3.8 per cent in 1941 and 6.2 per cent in 1945. At the same time the operability rate has increased from 62 per cent to 83 per cent.

Twenty-eight deaths occurred in the group of patients whose growths were so extensive that only laparotomy or colostomy was possible.

In the group of 73 patients in whom there was no evidence of involvement of the liver or lymph nodes at the time of resection, 31 patients were known

(Not Restricted)

to be living and well 10 or more years following their operation. At the end of 5 years following operation 36 patients were living and well without evidence of recurrence. Five patients died from recurrence of the carcinoma between their fifth and tenth postoperative years. Twenty-four patients died from recurrent carcinoma in from 1 month to 5 years following operation. Seven patients subsequently died from other causes, with no evidence of recurrence at the time of their death (5 of these 7 patients had survived without recurrence from 4 and 1/2 to 7 years after their resection). There were 6 postoperative or hospital deaths. The 1 patient with sarcoma of the rectum died from recurrent malignant disease less than 18 months after his operation. Omitting the 6 postoperative deaths and the 7 patients who died from causes other than the recurrence of their carcinoma, the 5-year survival rate was 60 per cent and the 10-year survival rate was 51.6 per cent.

In 52 cases no metastases were noted in the liver at operation, but the carcinoma was found to have spread to the mesenteric lymph nodes on examination of the resected specimen. Of this group, 10 patients were living and well 10 or more years following their operation. Three patients died from a recurrence of their malignant disease between their fifth and their tenth postoperative years. There were 5 postoperative deaths and 4 other patients subsequently died from other causes, with no evidence of recurrence at the time of their death. Omitting the postoperative deaths and the patients who died from other causes than malignant disease, the 5-year survival rate was 30.2 per cent and the 10-year survival rate was 23.2 per cent.

Although there was no difference in the length of survival of patients who had resection of their growth in the presence of liver metastases and those who had colostomy only (only 1 patient in each group lived more than 3 years), there was a marked difference in the postoperative clinical course. Those patients, in whom the rectal lesion was left in situ were usually very uncomfortable from the constant discharge of mucus and blood from the rectum, and they often had severe pain from sciatic and perineal nerve involvement. Those patients in whom the primary growth was removed were usually comfortable until within a few weeks of their death.

Of the 15 patients in whom the 10-year follow-up was incomplete and who were not included in the above analysis, 6 patients had had such advanced disease that only a laparotomy or colostomy was possible at the time of operation. Three other patients had resection in the presence of metastasis to adjacent lymph nodes or local extension of the growth. Thus, of the resected cases not known definitely to be palliative or unfavorable, only 6 were not followed for 10 years and 5 of these are known to have been living without recurrence from 6 to 8 years after operation. (Surg., Gynec. and Obst., July '47 - B. P. Colcock)

(Not Restricted)

The Frequency of Precancerous Lesions in the Rectum and Colon: The significance of benign polyps in the rectum and colon as precancerous lesions has been well established. However, the frequency with which polyps of the colon and rectum are found in patients and the indications for examinations of the colon and rectum have not been sufficiently emphasized. At the Lahey Clinic, as the indications for sigmoidoscopic and radiologic examinations of the rectum and colon have been broadened, the number of benign polyps discovered has increased.

Lawrence and Susman have reported an incidence of benign polyps of the colon and rectum varying from 2.3 to 6 per cent. In an attempt to emphasize the frequency of this premalignant lesion, a study has been made of the 1,843 autopsies performed in the pathological laboratory of the New England Deaconess Hospital between 1 January 1935 and 1 January 1944. The authors made this study to learn more about the incidence of benign polyps of the colon and rectum and to obtain additional information on the relation of these lesions to cancers originating in this region.

In 130 of the 1,843 bodies autopsied, 311 benign polyps were found - an incidence of 7 per cent. Two or more benign lesions were found in 55 (42 per cent) of the 130 bodies in which benign polyps were present; single lesions were found in 75 (58 per cent).

In the same autopsy series, 195 bodies were found to have 208 cancers. Benign polyps were present in 50 (25.1 per cent) of these 195 with cancers.

The locations of the cancers and the benign polyps are as follows:

	<u>Cancer</u>		<u>Benign Polyps</u>	
	Cases	Per cent	Cases	Per cent
Cecum				
Ascending colon	27	13.0	64	20.5
Hepatic flexure				
Transverse colon	28	13.5	85	27.3
Splenic flexure				
Descending colon				
Sigmoid				
Rectum	152	73.5	162	52.2
Anus				
Total	207		311	

(Not Restricted)

The incidence by age groups and sex of the cancers and the polyps were as follows:

Decade	<u>Cancer</u>		<u>Benign Polyps</u>	
	Males	Females	Males	Females
21-30	2	0	1	0
31-40	6	2	2	1
41-50	10	16	8	4
51-60	30	23	18	15
61-70	41	30	35	17
71-80 plus	23	15	21	12
Total	112	86	85	49

The authors recognize that because of various factors the 7 per cent incidence of polyps found in the colon and rectum cannot be considered the same as that which would be found in the population at large which they estimate to be from 3 to 5 per cent.

The ideal approach to the treatment of cancer of the large bowel is prevention. If it were possible to find and remove or destroy all polyps of the lower bowel before they become malignant, the problem would be simplified. Unfortunately, however, there are several difficulties to be overcome before this ideal can be accomplished.

It is true that over 50 per cent of all polyps of the colon and rectum are within reach of the 10-inch sigmoidoscope, as are 70 per cent of the malignant lesions. An analysis of patients with malignant disease of the large bowel reveals that an abnormal stool (primarily the presence of blood), any alteration in bowel function, unexplained abdominal pain, tumor or an unexplained anemia may indicate cancer of the colon or rectum. These findings demand complete examination of the rectum and colon. There is, however, no syndrome characteristic of cancer of the lower bowel. The detection of precancerous lesions is even more difficult if entire dependence is placed on symptomatology alone. The authors state that less than one-third of their patients present bleeding or any abnormality of their bowel function at the time of examination. The conclusion from this seems to be that a sigmoidoscopic examination should be carried out whenever possible for a complete physical examination. Each year an increase in the percentage of the authors' patients undergo sigmoidoscopic examinations and an increased incidence of precancerous lesions of the colon and rectum is discovered.

(Not Restricted)

The problem presented by patients with polyps above the reach of the 10-inch instrument is even more complicated. Diagnosis depends on radiologic study or direct examination of the bowel at the time of laparotomy. The ordinary barium enema roentgenogram for the detection of these tumors is not satisfactory. Careful preparation is imperative for any radiologic study of the colon. It is the authors' practice to administer 1 and 1/2 ounces of castor oil by mouth from eighteen to twenty-four hours before the examination. A low residue diet should also be given during this period. A few hours before roentgenologic examination the colon should be thoroughly irrigated. With this preparation, the contrast air enema technic of radiologic study of the colon which has been preceded by an ordinary barium enema roentgenogram is the best means available at present for the detection of polyps in the right and transverse colon. Experience has shown, however, that even with the contrast air enema technic a high percentage of polyps in the colon is not detected because of the difficulty in distinguishing small benign polyps in the colon from fecal concretions. It has also been the authors' experience that colotomy for the removal of these tumors is not justified until the diagnosis and exact location of the colon polyp or polyps have been verified by a confirmatory study.

Until better diagnostic means for the detection of tumors in the proximal colon are developed, repeated examinations must be carried out when polyps are suspected.

The high incidence of multiple tumors is important. When a single benign polyp is found every means should be undertaken to find and remove any other polyps that may be present. The frequent occurrence of more than one of these tumors is probably, in part at least, an explanation for the frequent occurrence of more than one malignant tumor in the large bowel. In this series multiple cancers were present in 8 (4 per cent) of the 195 bodies in which cancer was present at the time of autopsy. When it is remembered that 1 in 25 of all patients operated upon for cancer of the large bowel may have an additional malignant lesion at that time, the importance of careful examination of the entire colon and rectum before definitive treatment is carried out can be appreciated. When operating on patients for cancer of the colon and rectum, every effort must be made by palpation, sigmoidoscopic examination through the rectum and through colostomy stomas when indicated, and at times by the roentgenogram, to find and remove any additional benign polyps present. In this series, benign polyps were present in 25.1 per cent of the cases in which there was cancer of the colon or rectum. It is particularly important that patients who have had cancer of the large bowel should be followed indefinitely, and repeated attempts made to discover additional benign lesions of this type and remove them before they become malignant. Every surgeon has had the experience of having had a patient successfully operated upon for

(Not Restricted)

a large bowel cancerous lesion return years later with a second such lesion which was not a late recurrence but an entirely independent tumor which probably arose from a pre-existing benign mucosal polyp.

There has been a tendency in the medical profession to reserve for the rectal specialist sigmoidoscopic examinations of the rectum and lower part of the colon, and, even at times, a digital examination of the rectum. This has been due, in part at least, to the lack of training in this field in medical schools and in internships. It has been the belief at the Lahey Clinic for some time that there is no particular danger in a sigmoidoscopic examination. They have never had any injury result to a patient from the use of a sigmoidoscope, and examinations have been carried out by large numbers of physicians, many of whom had had little or no previous training in its use. The equipment required is inexpensive and simple to maintain. The authors believe that every physician doing general diagnostic work should appreciate the frequency of occurrence of these premalignant lesions and should be prepared to carry out sigmoidoscopic examinations. (Lahey Clin. Bull., Jan. '47 - N. W. Swinton and A. D. Haug)

\* \* \* \* \*

(Not Restricted)

The Stevens-Johnson Syndrome: Stevens and Johnson in 1922 described a "new" eruptive fever associated with stomatitis, ophthalmia, cutaneous eruption, and constitutional symptoms. This syndrome is usually considered uncommon; the authors have seen but 15 patients with it out of 115,000 patients admitted to the hospital since September 1942, six of whom had only simple catarrhal conjunctivitis and are not included in this report. This syndrome deserves more emphasis because tragic complications of the eyes, consisting of corneal ulceration or panophthalmitis with partial or complete loss of vision, have been frequent in reported cases. These severe complications of the eyes did not occur in 9 patients treated by the authors with sulfonamide drugs and/or penicillin.

The Stevens-Johnson syndrome has been referred to as erythema multiforme bullosum with involvement of the mucous membranes of the eyes and mouth, erythema exudativum multiforme with ophthalmia and stomatitis, or severe erythema multiforme.

The causation of this syndrome is unknown. Many factors have been suggested as playing a part; various micro-organisms and drugs including the sulfonamides have been thought to be the etiologic agent. Hemolytic Staphylococcus aureus and Vincent's organisms have been among the bacteria most commonly believed to be causative. In this series, both organisms were found, but the authors believe that they were secondary invaders.

(Not Restricted)

The syndrome consists of an acute illness accompanied by the appearance of vesicular, bullous, and ulcerative lesions on the mucous membranes, most characteristically those of the eyes, nose, mouth, tracheobronchial tree, esophagus, anus, and genitalia. Lesions of the skin may or may not be present and are either erythematopapular or vesiculobullous in nature, but, when present, are of the type seen in an ordinary case of erythema multiforme. The patients may be seriously ill, or they may have only a few systemic symptoms. Fever may or may not be present, and the degree of elevation of the temperature varies considerably. Recurrences have been frequent, and generally the later attacks are less severe than the initial one. Most of the patients are in the younger age group.

Almost all the mucous membranes have been reported to be the site of appearance of the lesions. Conjunctivitis, rhinitis, stomatitis, pharyngitis, tracheobronchitis, urethritis, balanitis, hematuria, generalized lymphadenopathy and splenomegaly, and lesions of the anal mucosa have been reported.

With such a multiplicity of sites involved, the possibilities of complications are great. The most dramatic complications are to be found in the eyes, where decided purulent conjunctivitis leads at times to perforation of the cornea and the development of panophthalmitis, with total loss of vision, or to corneal scarring with diminution of visual acuity or chronic conjunctivitis and the formation of symblepharon, with subsequent distortion of the eyelids. Therefore, early diagnosis and institution of treatment designed to prevent permanent ocular involvement are imperative.

In the differential diagnosis, the most important conditions to be ruled out, as Lever indicated, are foot and mouth disease, Vincent's angina, drug eruptions, pemphigus, venereal penile lesions and urethritis. Drug eruptions may be difficult to distinguish. The lesions may be identical in appearance, but the history, the notable systemic involvement and the course should aid in differentiation. In considering drug eruptions, it is of interest that the sulfonamide drugs have been implicated as precipitating factors or specific causes in some cases of erythema multiforme bullosum. One patient in the authors' series had been given sulfadiazine several weeks prior to the onset of the Stevens-Johnson syndrome. He had experienced three previous attacks but had received no sulfonamide drugs prior to any of those. The use of the sulfonamide compounds by the authors did not appear to aggravate the lesions but rather had the directly opposite effect. The appearance of foot and mouth disease is clinically similar to that of the Stevens-Johnson syndrome. According to Klauder, the differentiation depends on the inoculation of laboratory animals when foot and mouth disease is suspected. Vincent's angina does not cause the large bullous lesions on the mucous membranes so characteristic of the Stevens-Johnson syndrome. Pemphigus vulgaris has an onset and course

(Not Restricted)

entirely different from that of erythema multiforme bullosum. Penile lesions require a darkfield examination and serologic analysis of the blood. These tests were negative in the authors' cases. The appearance of the rash on the skin, and the bullous involvement of other mucous membranes should establish the differential diagnosis. In patients complaining of urinary symptoms, the determination of the presence of a urethritis as a separate entity or as a part of the general picture offers no difficulty.

According to Lever, only 4 fatal cases of the Stevens-Johnson syndrome have been reported in the world's literature.

Until recently, treatment has consisted in supportive and symptomatic measures. It was reported that in five patients in whom either sulfonamide drugs or penicillin were employed in treatment, 4 made complete recoveries. Givner reported 2 patients with this syndrome, and in both, one of the sulfonamide drugs had been given therapeutically, and complete recovery ensued. He added a third case of a patient under treatment at the time his paper was being written. Erger reported one case of a patient treated with sulfadiazine in whom corneal scarring developed; Kove reported the cases of 2 patients, both of whom made complete recoveries, both of whom received sulfadiazine and one of whom had penicillin instilled in the eye in addition. Of the author's 9 patients treated with sulfonamide compounds and/or penicillin, 8 made complete recoveries; in one chronic conjunctivitis and mild symblepharon developed but without evidence of corneal scarring. (Arch. Int. Med., May '47 D. O. Wright et al.)

\* \* \* \* \*

(Not Restricted)

Toward Resolution of the Complexities of the Rh Problem: The importance of the Rh problem to the average clinical pathologist is of such magnitude as to make necessary an understanding of its many complexities. The new knowledge in this field is significant not only to other branches of medicine dealing with transfusion or childbirth, but also to the fields of immunology, hematology, genetics, and physicochemistry. It is unfortunate that, for a second time, since blood types were discovered in 1900, the nomenclature of blood factors has been confused by multiple systems of terminology, and the naming of this antigenic factor present in the red cells of human beings as the Rh factor because of its resemblance to a similar, but not identical one, discovered in the rhesus monkey by Landsteiner and Wiener, was, in itself, confusing.

The Rh factor in human beings was first reported but not named in 1939. A "dominant property" in the fetus inherited from the father and responsible for iso-immunization of the mother was postulated. The conclusion that this

(Not Restricted)

agglutinin was inherited as a simple Mendelian dominant was supported by the family studies made by Landsteiner and Wiener. It should be noted in passing, however, that had Levine's anti-Hr serum been discovered first, a similar theory of inheritance of a dominant factor (Hr) could have been proposed equally well. Such a theory, however, would have required diametrically opposed conclusions with the recessive character now becoming dominant and the previously dominant character becoming recessive. The subsequent discovery of many Rh antibodies has strongly suggested that all Rh antigens may be determined directly by the use of the appropriate antiserum. Accordingly, in the light of present knowledge, it seems best to abandon all concepts of dominance of Rh genes, whether relative or absolute, and simply consider all Rh types as determined by allelomorphic genes without dominance.

The understanding of the Rh problem, to those who attempted to follow it, seemed beset with difficulties from the very start. For example, it was only shortly after the various Rh antibodies were first recognized and named that new data required a complete change in their designation. In the naming of Rh genes and antigens and in the formation of subtype classifications, new designations having as their purpose the explanation of new data or the simplification and clarification of the known facts have appeared in the literature at frequent intervals. The various efforts intended to simplify and clarify have not been entirely successful, particularly from the point of view of helping to solve clinical and laboratory problems encountered in cases of iso-immunization.

The classification of Murray represents an ingenious attempt to designate all Rh-Hr antigens in a purely descriptive manner by noting their reactions to the different Rh antisera as required by Fisher's theory. Snyder's classification, on the other hand, appears to be a simplification in the method of designation according to Wiener's classification to conform with usual genetic practice. With the exception of the brief and incomplete initial classification of Wiener and Landsteiner, the remaining classifications are those of Wiener. These classifications indicate a remarkable effort to systematize the known facts of the reactions of the Rh antigens into schemes comparable to the four blood groups of Landsteiner (International classification). Accordingly, the four Rh groups were designated W, U, V, UV, as determined by two sera (anti-Rh' and anti-Rh''). Further characterization into eight subgroups became apparent through the use of an additional serum (anti-Rh<sub>0</sub>). In the three latest classifications of Wiener, these same eight subtypes are continued with slight changes in the symbols designating the individual types. Furthermore, information obtained from extensive family studies was utilized in the integration of gene designation and the theory of inheritance. This theory postulated inheritance according to Mendelian dominance of six allelic genes, presumably occurring at one locus in each chromosome. One gene was considered dominant

(Not Restricted)

to another. For example, the gene  $Rh_1$  was dominant over  $Rh_2$  and  $rh$ , and  $Rh_2$  was dominant over  $rh$ .

One of the most confusing difficulties encountered by many who attempted to use or teach this theory and classification was its failure to explain the significance of the antigen determined by Levine's anti-Hr serum. Levine designated this antiserum Hr because of an apparent reciprocal or antithetical relationship between the antigen which it identified and the then designated Rh antigen. This relationship was not clear until Levine recognized that the Hr and  $Rh'$  antigens seemed to be related in the same manner that the M and N blood antigens of red blood cells were related.

In England, Race and Taylor had noted that their St serum (subsequently designated anti-c) could be used to determine whether an individual was homozygous ( $RhRh$  of that time) or heterozygous ( $Rhrh$ ) by negative or positive reactions, respectively. This serum has been shown to possess the same characteristics as Levine's anti-Hr. Later when the serum now termed anti-C or anti- $Rh'$  was used, the antithetical relationship of  $Rh'$  and Hr shown by Levine was discovered independently by Race, Taylor, Cappell and McFarlane. On this basis, Fisher assumed that these two antigens were determined by two allelomorphous genes at one locus (i.e., either gene present at this point in one chromosome). But, a lack of a similar relationship of the other Rh antigens to each other or to the then known Hr antigen indicated the possibility of two additional loci on the same chromosome. The arrangement proposed by Fisher is shown in Fig. 1.

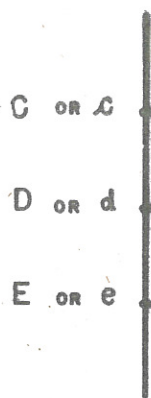


FIG. 1. CHROMOSOME MAP SHOWING POSSIBLE LOCATION OF CDE-cde GENES

cde/cde (Rh-)	CDe/CDe ( $Rh_1 Rh_1$ )	CDe/cde ( $Rh_1 rh$ )	CDe/cDE ( $Rh_1 Rh_2$ )	Cde/cDE ( $Rh' Rh_2$ )
14.4%	17.2%	33.0%	11.2%	2.0%
3 antigens	3 antigens	5 antigens	5 antigens	6 antigens

Three points on the chromosome, named C, D, and E, represent the separate but closely placed locations of genes determining the Rh antigens. The

(Not Restricted)

alternative (allelomorphic) gene possible at each locus is designated c, d, or e (determining the three Hr antigens). Thus, the place of the original Hr factor (Hr' or c), as well as the more recently discovered anti-d (Hr<sub>0</sub>) and anti-e (Hr'') become completely clarified. As a matter of fact, this theory predicted the existence of these additional antigens and antiserums and thus made their discovery easier.

Figure 2 below shows some typical chromosome pairs with the arrangement of the genes determining the CDE (Rh) antigens. It will be seen that the number of antigens may vary from a minimum of three, when homozygous at all three loci, to a maximum of six, when heterozygous at all loci.

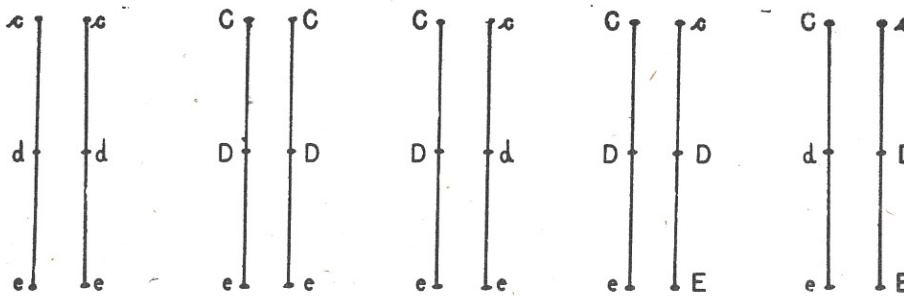


FIG. 2. TYPICAL CHROMOSOME PAIRS DETERMINING RH ANTIGENS (GENOTYPES)

Examination of possible arrangements of genes in chromosome pairs according to this theory quickly reveals fascinating possibilities for the clinical pathologist in the study of specific problems. However, in order to estimate the actual CDE gene arrangements (genotype) in a patient without making family genetic studies, it is necessary to have an idea of the incidence of a few of the most common CDE chromosomes. For example, a patient whose erythrocytes contain the C, D, and E antigens as determined by the corresponding three antiserums, probably has the chromosomes CDe/cDE because the incidence of the chromosome CDE (R<sub>Z</sub>) is only .13 per cent compared with an incidence for CDe of 43.6 per cent and for cDE of 12.8 per cent. Even with six antiserums, C, D, E, c, d, e, it would still be necessary to use chromosome frequencies to estimate genotypes since each individual has a total of six genes on two chromosomes. Fortunately, the odds for a correct assumption are very good when this method is used in connection with the four antiserums C, D, E, and c now available for clinical use. The table following shows the possible chromosome arrangements under the Fisher-Race theory and their incidence. From this table it may be noted that, in practice, it is only necessary to know that the three chromosomes listed to the left of the double line are the common ones. In any usual situation where alternative chromosomes are possible to explain the antigens determined, the odds are better than from 12 to 1 in favor of the three common chromosomes over the rarer ones.

(Not Restricted)

FREQUENCY OF GENE ARRANGEMENTS ON CHROMOSOMES AND INCIDENCE (ACCORDING TO FISHER'S THEORY)

PER CENT POSITIVE WHITE BLOODS (SPECIFICITY)	ANTIBODY DESIGNATION	COMMON			RARE				
		CDe 43.6 per cent	cde 37.9 per cent	cDE 12.8 per cent	cDe 3.0 per cent	cdE 1.7 per cent	Cde 0.8 per cent	CDE*	CdE**
70	Anti-C	+	-	-	-	-	+	+	(+)
85	Anti-D	+	-	+	+	-	-	+	(+)
30	Anti-E	-	-	+	-	+	-	+	(+)
80	Anti-c	-	+	+	+	+	-	-	(-)
65	Anti-d	-	+	-	-	+	+	-	(+)
96	Anti-e	+	+	-	+	-	+	-	(-)

\* Calculated by Race, 0.13 per cent.

\*\* Predicted.

Bearing in mind the immunologic principle that an individual can be immunized only against antigens he does not normally possess, it is simple to visualize any CDE-cde (Rh-Hr) incompatibility, or iso-immunization problem due to pregnancy. For example, a patient was recently admitted to Baylor Hospital for treatment of a hemolytic transfusion reaction caused by administration of 380 c.c. of husband's blood for hemorrhagic shock following delivery of a slightly icteric infant. Owing to continued hemorrhage as well as the hemolytic reaction, the patient was in desperate need of compatible blood. Both husband and wife had been typed as Rh-positive elsewhere. A retyping with anti-C, D, E, c, and e serums showed the following:

	ANTISERUM					ANTICIPATED GENOTYPE
	C	c	D	E	e	
Mrs. A.....	-	+	-	-	+	cde/cde
Mr. A.....	+	+	+	+	+	CDe/cDE
Infant A.....	-	+	+	+	+	cde/cDE

The genotype of the mother was obviously cde/cde (Rh-negative), and the husband's genotype, as anticipated, was shown to be CDe/cDE when the infant's blood examined later was found to be cDE/cde. From this, it is apparent that the mother could have been immunized against D or E, or both, by the infant and by C, D, or E from the husband's blood. The antibodies present were anti-D with development later of anti-C as a result of the transfusion. The infant's red cells contained only D and E antigens to the three standard serums and were strongly positive to anti-c serum. Note that the husband's genotype, CDe/cDE, having genes CD on one chromosome and DE on the other has the clinical significance that any future pregnancy would result in an erythroblastotic infant.

In another case to be reported in detail elsewhere, the author and co-workers were presented with the problem of supplying blood for an urgently needed transfusion

(Not Restricted)

in a pregnant woman (in another state) who had had a hemolytic reaction to transfused blood from a donor, not her husband. One child was living and one premature infant had died. Several transfusions had been given prior to the reaction. The mother was type A, with anticipated genotype CDe/CDe by use of anti-C, D, E, and c serums. The father was expected to be CDe/cde and the living child CDe/cde. The patient had received transfusions of blood of probable genotypes CDe/cDE, cDE/cDE, cDE/cde in the order listed. Note that the rare anti-e serum of Mourant was not actually necessary in the management of this case, although it was essential to complete the genotyping of the second (cDE/cDE) and third (cDE/cde) bloods of the series given. An antibody demonstrable only with the developing test or Diamond's albumin method was too weak for accurate determination but appeared to be anti-c or d. From the estimated genotypes, it is obvious that the patient might have been immunized by c, d, or E. For this reason it was decided to give only blood negative for these antigens, that is, the same as that of the patient. In choosing such bloods of identical genotype it was necessary to use the method of predicting probable genotypes, using only the four serums anti-C, D, E, and c, since anti-D was not available. No difficulty resulted from giving four pints of blood selected in this manner. The use of the Fisher-Race concept and the method of estimating genotypes greatly facilitated the management of this case.

The following table includes an arrangement of the more common genotypes encountered by the clinical pathologist in practice. Again it may be noted that all major genotypes may be estimated by use of anti-C, D, E, and c serums presently available for clinical use. A possible exception of some importance in obstetric practice is the instance in which differentiation between the homozygous cDE/cDE and heterozygous cDE/cde is desired. For this purpose the rare anti-e serum would be required.

ESTIMATED GENOTYPES  
(Rare types omitted)

Determined by anti-C, D and E	HETEROZYGOTE	HETEROZYGOTE
	Determined by anti-c	Determined by anti-e
cde/cde	Cde/cde	cdE/cde
Cde/Cde		
cdE/cdE	CDe/cde	cDE/cde
cDe/cde		
CDe/CDe		
cDE/cDE		
CDe/cDE		

For practical application by clinical pathologists, it seems that the use of the Fisher-Race concept and nomenclature can be of the greatest value. Although it may take some period of time for the accumulation of sufficient evidence to satisfy geneticists concerning the ultimate correctness of the different theories of inheritance and systems of nomenclature, the clinical

(Not Restricted)

pathologist is daily confronted with problems which he can solve more easily by the concept of Fisher and Race. In practical application with a large transfusion service, in teaching medical students and technicians, and even in explaining incompatibility problems of erythroblastosis or of transfusions to patients, the authors have found the CDE system to be most satisfactory. This experience includes the use of anti-C, D, E, C<sup>W</sup>, D<sup>u</sup>, c and e serums.

The adaptability of the Fisher-Race concept is well illustrated, first, by making possible the prediction of types of antigen combinations and anti-serums not previously observed and, second, by the incorporation of the unpredicted additional rare allelomorphic genes C and D at the C and D loci. It is perfectly possible that rare additional allelomorphic genes may be found at the E locus also. At present, the clinical pathologist need not concern himself with these recently discovered antigens because of their rarity and the scarcity of the antisera. A further observation based on statistical studies is Fisher's suggestion that the order of the genes on the chromosome may be D, C, and E. The order of genes in the chromosome makes no difference whatsoever for clinical use but it is of interest genetically. (Am. J. Clin. Path., June '47 - Editorial - J. M. Hill)

\* \* \* \* \*

(Not Restricted)

A Survey of Commercial Rh Antiserums: The increasing recognition of the importance of the Rh factor in medical practice has taken the testing for this blood factor out of the hands of the specialist and placed it in the realm of the medical technician in the hospital and in the doctor's office. Despite the marketing of diagnostic antiserum by numerous commercial laboratories, the demand for such antiserum has been so great that it is often not available for purchase. Such a situation must inevitably lead to some carelessness in production unless there is some central control of the assay, labeling and standardization of Rh antiserum.

The authors were impressed with the problem when they began a survey for the presence of the Rh factor in pregnant women at the White Memorial Hospital, Los Angeles. The varying quality of different serums soon became obvious. Before beginning the main study, a comparison of various commercial antisera seemed necessary. The findings are reported here.

Six different Rh antisera from four different manufacturers were tested on a series of bloods from patients. The results varied from 10 per cent to 100 per cent positive, instead of from the theoretical variation of from 85 to 87 per cent.

(Not Restricted)

The variations which were present in the serums tested might have been due to a number of causes. First, deterioration might have occurred between the time the serum left the manufacturer and the time it reached the laboratory. All serums were used before the expiration dates printed on the container. There was, however, no uniformity in the expiration periods which were set. Each of two powdered preparations had an expiration period of thirty days. One liquid preparation had a three-month period and another a six-month period before expiration.

Because the authors' experience indicates that deterioration did occur, it is considered that more study is essential to determine the optimum conditions for preservation.

Another problem concerns the initial strength of the serum. Although there is no definite relation between the titer of the serum and the number of Rh-positive bloods, nevertheless, the strength of the serum must play a role in the accuracy of the test. No data were given for control titration of the serums examined.

The actual details of procedure might have accounted for some error, but instructions were followed in each case. If the procedures required a more meticulous technic than that employed, the authors then believe that the test was too sensitive for routine work. If the results are not read microscopically, as for example in the test tube method, accuracy decreases. Philip Levine advises, contrary to the instructions of one commercial concern, that tests should be run only by qualified technicians and not by the physician himself in his spare time.

A final source of difficulty has to do with the terminology of the subgroups of the Rh factor (see preceding article). In the United States, Wiener and Philip Levine lead two schools of thought on the correct genetic interpretation of the Rh phenomenon and the terminology of the subgroups. It is essential for the whole problem to be clarified so that the laboratory worker will know, at least, the practical aspects of the terminology. At the international conference recently held in Dallas, Texas, most workers seemed to support the British terminology, which is in accordance with Levine's theory.

To illustrate the confusion in the labeling of commercial serums, one product, an "87 per cent positive" serum, is listed as anti-Rh<sub>0</sub>' which certainly does not conform to any terminology. Taken literally, it is a serum against the Rh<sub>0</sub> and Rh' factors and does not include the Rh" group and, therefore, should fall short of giving 87 per cent positive findings.

(Not Restricted)

A definite need for standardization and control of Rh diagnostic anti-serums is indicated. (Am. J. Clin. Path., June '47 - M. G. Levine and R. E. Hoyt)

\* \* \* \* \*

(Not Restricted)

Autohemagglutination and Raynaud's Syndrome: Autohemagglutinins in a person's serum will produce agglutination of his own corpuscles at temperatures below that of the body. They are most active at 0° C., less active at room temperature, and inert at body temperature. Autohemagglutinins are capable of agglutinating at low temperatures not only autologous corpuscles, but also those of other individuals irrespective of their blood group, and in some cases the corpuscles of various animals as well. The reaction is reversible. Corpuscles which have been agglutinated at low temperatures will disperse on heating to body temperature and reagglutinate on cooling.

The association of autohemagglutination with symptoms of a peripheral vascular nature has been observed on several occasions. Iwai and Mei-Sai in 1925 and 1926 reported two cases of Raynaud's syndrome with associated auto-agglutinins of high titer and were of the opinion that the peripheral vascular manifestations in their cases resulted from intravascular hemagglutination when the extremities were subjected to low environmental temperatures.

In 1937 McCombs and McElroy reviewed the literature on autohemagglutination with special reference to its association with Raynaud's syndrome. They were able to collect five case reports of this association, and added one more to the list themselves. According to Stats and Bullowa (1943), 14 accounts of this combination of phenomena had appeared in the literature by 1943. To these the author adds four other case reports. They are by LeGoff (1933), Ernstene and Gardner (1935), Davidsohn (1942), and Helwig and Freis (1943).

Laboratory findings are emphasized in most of the accounts in the literature and full clinical details are not always available. Intermittent pallor or cyanosis of the extremities, precipitated by exposure to cold, is the predominant clinical feature, and the presence in the blood of agglutinins which react to high titer in the cold is a constant laboratory finding. Attendant clinical features such as anemia, hemoglobinuria, hepatic dysfunction, and organic occlusive disease of the peripheral vessels are found in the case reports. Males are affected more often than females and there is wide variation in age incidence. Few, if any, of the patients appear to have been suffering from the true clinical entity called Raynaud's disease.

(Not Restricted)

The author recently investigated the case of a 24-year-old American sergeant who was admitted to the hospital with the complaint that his fingers became blue and numb on exposure to cold environmental conditions. He had had several attacks in the course of a few days before admission, during which time the weather was moderately cold. An attack would develop if his hands were uncovered while out of doors or in bed at night. Each attack would last for from 10 to 20 minutes and would be rapidly relieved by warmth. He stated that changes first appeared at the tips of his fingers. Usually the tip of one finger of either hand would first become involved and the change would gradually extend to all the fingers of one or both hands. The palms and the dorsa of the hands were affected to a less degree than the fingers; the wrists and forearms were unaffected. Color changes during an attack were rather variable and depended to a certain extent on whether he was in the upright or the recumbent position, and whether or not he took immediate steps to alleviate the condition. From his description it seems that the fingers assumed a mottled dusky tint with white and purple patches and areas of normal coloring. In one attack the white patches would predominate, in another the purple. During the recovery phase the fingers would become first pale orange in color, gradually intensifying to red and then fading to the normal skin coloring. He stated that his fingers felt numb during an attack and that they "throbbled" for a short time afterwards. Occasionally the tip of his nose and the lobes of his ears would become blue. His toes and feet were not affected at any time.

That the patient was an "auto-agglutinator" was first suspected when an attempt was made to do a blood count. Capillary blood issuing from a small puncture wound in the lobe of the ear was seen to agglutinate spontaneously, and large clumps of corpuscles were present in the diluting pipette. Under these circumstances it was impossible to carry out an accurate blood count, but by warming the patient's ear with a hot-water bottle and using pipettes and diluting fluids which had been warmed to 37° C. before use agglutination was temporarily prevented and a reasonably accurate blood count obtained.

It was shown experimentally that the abnormal agglutinin in this patient's serum was a true autohemagglutinin. The disease or factor responsible for its presence was not, however, determined. The fact that no abnormality was detected on physical and radiological examinations of the chest does not altogether exclude the possibility that the patient had suffered recently from a subclinical attack of primary atypical pneumonia, a disease which was encountered not infrequently among Service personnel in northwestern Europe at the time of his admission. It is known that primary atypical pneumonia may assume a very mild subclinical form. Turner et al. in 1943 recorded a case of the disease in an ambulant female patient whose only complaint was of a bad cough. Her chest was roentgenographically negative, and her blood

(Not Restricted)

serum contained agglutinins that were active at a lower than body temperature to a titer of 1:1000.

There can be little doubt that the peripheral vascular manifestations in the case studied were due to mechanical blockage of the small peripheral vessels by aggregations of corpuscles within them, the activating factor being exposure to cold. Cold exerted its influence by (a) lowering the temperature of the exposed extremities to the critical level for auto-agglutination and (b) producing simultaneously a constriction of these vessels. The affected vessels were thus almost completely occluded and the clinical features of Raynaud's phenomenon were produced. In true Raynaud's disease obliteration of the vessel lumen is brought about by intense spasm of the vessel. Although the mechanism of production of vascular obliteration is different in the two conditions the end-result is essentially the same. The peripheral vascular manifestations readily disappeared when heat was applied to the affected extremities, owing presumably to dilatation of the peripheral vessels and dissolution of the corpuscle aggregations. A free flow of blood to the parts was thus re-established.

The patient informed the author by letter three months after his discharge from the hospital that he was then symptom free and that a blood examination for cold and auto-agglutinins was negative. (Brit. M. J., May 3, '47 - G. B. Forbes)

\* \* \* \* \*

(Not Restricted)

The Composition of Urinary Calculi: The problem of urinary lithiasis remains unsolved despite a vast amount of clinical observation and experimental research. The factors of causation can only be stated in terms of broad and indefinite generalization and are believed to be linked with nutrition. Numerous specific exceptions to such factors are known to exist. Among a people with a high standard of nutrition, the proposition becomes increasingly difficult. Prevention of calculus in the population at large may be dismissed without consideration in the light of our present knowledge. Prevention of recurrence in the susceptible individual, on the other hand, demands our best efforts - and we have not been too successful.

In seeking new approaches to the problem of recurrence it has become apparent that there exists a lack of basic and fundamental knowledge concerning the exact composition of urinary calculi. This is largely due to inadequate methods of analysis. In the present study an attempt has been made to supply this deficiency. Succeeding papers will be offered on various other aspects of the problem of calculus.

(Not Restricted)

Because all urinary calculi are crystalline (exception: extremely rare fibrin and bacterial calculi), it was considered that they should be amenable to analysis by the modern physical technics used in the study of minerals. These methods include the use of polarized light (optical crystallography) and x-ray diffraction photography (x-ray crystallography).

Examination by polarized light is done by means of the petrographic microscope. Polarized light is influenced by transmission through transparent grains of coarsely powdered calculus and these changes in the light are measured by the microscope and may be recorded as the optical constants of the substance. The optical constants depend upon the atomic structure and are distinct, invariable, and characteristic for any particular crystalline substance and constitute a rigorous means of identifying it. By preparing a table of optical constants for known compounds it is possible to identify unknown compounds by comparing their constants with such a table. Only a minute amount of calculous material is required for a complete examination.

Examination by x-ray diffraction photography consists in irradiating very finely powdered calculous material by a beam of monochromatic x-rays and recording the rays diffracted (reflected) from the crystal planes upon a photographic film as a series of lines of variable spacing and intensity, producing what is known as a "powder pattern." Such patterns are characteristic for each substance and offer a rigorous means of identification. They are identified by comparing them with the previously prepared patterns of known substances. X-ray diffraction study is not practical in the routine analysis of calculi because it is expensive and time-consuming. In the initial investigative phase of the present study optical analysis and x-ray study were used to corroborate and supplement each other.

In routine analysis the calculi are first fractured and dissected with a pointed tool under low magnification with ordinary light. Samples of material are carefully selected from the nucleus, various layers, etc., powdered, and identified upon the polarizing microscope. Optical analysis is simple, rapid, approximately quantitative, rigorously accurate and applicable to all calculi, including those of microscopic size.

Many supposed constituents of calculi as recorded in the medical literature were found to be nonexistent when sought by these modern physical methods of identification. The following reasons are adduced in explanation of this situation: a) confusion exists concerning the exact nature of the reactions which take place in the procedures used in chemical tests, b) interfering organic substances of unknown composition may invalidate these reactions, c) the complex nature of the phosphates in calculi is not amenable to

(Not Restricted)

resolution by chemical methods alone, and d) the small size of many calculi makes complete chemical examination impossible.

The crystalline components of urinary calculi (as found in this study) are: calcium oxalate monohydrate (whewellite), calcium oxalate dihydrate (weddelite), magnesium ammonium phosphate hexahydrate (struvite), carbonate-apatite and hydroxyl-apatite (collectively called apatite), calcium hydrogen phosphate dihydrate (brushite), uric acid, cystine and sodium acid urate. The authors give the appearance, associations and optical constants of these substances and present a determinative table, photographs, x-ray diffraction photographs, and x-ray spacing data. Calcium carbonate, cholesterol, xanthine and indigo were not found in a series of approximately 700 calculi.

Pure calcium oxalate calculi constituted 36.1 per cent of the total; mixed calcium oxalate-apatite calculi comprised 31.0 per cent; together they composed 67.1 per cent of the total. These calculi usually (but not always) occur in acid sterile urine. Pure magnesium ammonium phosphate hexahydrate, pure apatite and mixed magnesium ammonium phosphate hexahydrate-apatite calculi comprised 19.5 per cent of the total. These calculi usually (but not always) occur in alkaline infected urine. Calcium hydrogen phosphate dihydrate occurred in 1.6 per cent of the calculi. Uric acid and cystine exist more frequently in pure than in mixed form and occurred in 6.1 per cent and 3.8 per cent respectively of the series. Sodium acid urate occurred but once in the series and in microscopic amount. It was the only urate found.

The methods of optical and x-ray crystallography provide powerful tools for study of various aspects of calculous disease. (J. Urol., June '47 - E. L. Prien and C. Frondel)

\* \* \* \* \*

(Not Restricted)

#### Experimental Production of Kidney Stones with Urea-Splitting Organisms:

The importance of infection as the cause of some primary and recurrent urinary calculi is well known. In 1940 Chute and Suby reported from the Massachusetts General Hospital stone clinic that 54 per cent of urinary stones were associated with infection of the urinary tract by urea-splitting organisms.

The part that infection plays in the formation of urinary calculi is dependent on the fact that certain bacteria possess the power to split urea, form ammonia, alkalize the urine, and precipitate calcium phosphate. Many bacteria possess this property. Proteus vulgaris, Hemophilus influenzae, Pseudomonas aeruginosa, some strains of staphylococcus, streptococcus, Escherichia coli,

(Not Restricted)

and others have been proved thus to alkalinize the urine. By culturing bacteria on special media containing urea and a color pH indicator, it is possible to determine whether the bacteria tested split urea and produce ammonia.

It has been a clinical observation that many urinary infections are secondary to sepsis elsewhere in the body, such as sinusitis, osteomyelitis, or dental infections. It is not unreasonable, therefore, to suppose that in these cases of sepsis there has been a transient bacteremia whereby the infection has spread to the urinary tract.

In 1925 Rosenow reported that "specific bacteria" had produced urinary stones experimentally in dogs. In this report, however, there was no detailed record of the hydrogen ion concentration of the urine.

A most instructive study in experimental pyelonephritis was reported by Kenneth Mallory of the Boston City Hospital. He partially ligated ureters of rabbits and gave them intravenous injections of known amounts and types of bacteria. The course of the resultant kidney infection was followed by variously timed postmortem examinations. Urinalyses, however, were not done throughout this study.

In view of these observations several experiments on rabbits were started. One purpose of these experiments was to note the effect of intravenous injection of urea-splitting organisms on the urine pH of rabbits with normal and with hydronephrotic kidneys. Bacteria from urines of patients with kidney stones and from foci of infection of patients with kidney stones were used. The other purpose was to obtain a favorable method of producing pyelonephritis and renal calculi in animals which would simulate this disease in man, and which could be used in experimental problems of urinary infection and stone dissolution in normal and abnormal kidneys.

Organisms recovered from the urine of patients suffering from calcium phosphate urinary calculi were injected intravenously in rabbits which had been given an artificial hydronephrosis.

Immediately following injection of urea-splitting organisms the voided urine became strongly alkaline. The urinalyses and pH determinations were then followed from 3 to 4 times a week, and roentgenograms were taken at weekly intervals. In animals injected with bacteria which did not split urea, a urinary infection developed but the rabbit continued to pass an acid urine.

Animals with no artificially produced abnormality of the urinary tract, when given intravenous injections of urea-splitting organisms, voided a markedly alkaline urine for from 12 to 24 hours, but the urine then again

(Not Restricted)

became normal and acid. Similarly, normal female rabbits which were catheterized, and into whose bladders pure cultures of Proteus vulgaris were introduced, voided an alkaline urine which became normal and acid again after 2 or 3 days.

Approximately 60 rabbits were given artificial left hydronephrosis and pyelonephritis. Various degrees of stone formation were obtained.

One of these rabbits, with urine of pH 5.5, was given intravenously 0.25 c.c. of a 48-hour growth of Proteus vulgaris recovered from the urine of a patient with bilateral renal stones. Two days later the urine showed pH 7.5. One month later, a roentgenogram revealed faint stone shadows in the left kidney region and at autopsy 4 and 1/2 months after the infecting dose of organisms large stones were found in the left kidney.

Another rabbit injected with 0.25 c.c. of a 24-hour culture of a Staphylococcus albus from a tooth socket of a patient with urinary infection and renal calculus ran a similar course, and at autopsy 5 months after the infecting dose of organisms showed a large and soft left renal stone. The patient from whom the staphylococcus was obtained had been perfectly well until he had a tooth extraction for an abscess. Concomitant with this infection urinary symptoms which proved to be pyelitis developed. Since then his urine had shown many pus cells in the sediment, and the patient had had recurrent attacks of bilateral flank pain. Four years after his first urinary symptoms he was admitted to the M. G. H. and was found to have bilateral renal calculi. His urine was mildly alkaline and repeated cultures showed Staphylococcus albus. At this admission he was found to have another apical dental abscess. At tooth extraction cultures of tooth sockets revealed Staphylococcus albus. The cultural characteristics of the organisms from the tooth and urine seemed the same. A blood culture taken immediately following tooth extraction was sterile.

This method of producing kidney stones in animals furnishes a means for further experimental study on calcium phosphate urinary stone dissolution. (J. Urol., June '47 - H. I. Suby and R. M. Suby)

\* \* \* \* \*

(Not Restricted)

The Neuromuscular System in Rheumatoid Arthritis: Muscle weakness, usually associated with atrophy, constitutes one of the most disabling features of rheumatoid arthritis. If the muscle atrophy becomes established, it undoubtedly contributes to joint deformity and presents a major hindrance to the regaining of the normal joint function. In addition, early in the disease,

(Not Restricted)

motor weakness, often accompanied by numbness and paresthesias, may strongly suggest the diagnosis of a primary neurologic disorder. The problem of muscular atrophy in arthritis has attracted the attention of numerous clinical observers and has led to animal experimentation in an attempt to elucidate its origin. Since rheumatoid arthritis cannot be reproduced in animals, the present investigation is entirely upon the human subject and utilizes both electromyographic tracings and histologic studies of the central nervous system, the peripheral nerves, and the voluntary muscles.

Electromyographic studies were performed on patients with rheumatoid and other forms of arthritis. In addition, postmortem histologic observations were made of the central and peripheral nervous system and of the muscles in rheumatoid arthritis.

Tracings of voluntary muscle contractions showed no constant deviation from those of normal controls. Synchronization of motor unit leads and spread of tendon reflexes, important electromyographic characteristics of upper motor neurone lesions, could not be demonstrated in patients with rheumatoid arthritis. Involuntary skeletal muscle activity was inconstantly present in 50 per cent of 34 patients with rheumatoid arthritis, consisting usually in a series of regularly recurring diphasic spikes, believed to represent contractions of a single motor unit. A closely similar pattern has been observed in anterior poliomyelitis, peripheral nerve injuries, infectious polyneuritis and spinal cord lesions (tumors and ruptured intervertebral disks). In 8 patients, regularly recurring spikes were not recorded after procaine block of the motor nerve supply to the muscle examined. This finding places their origin above the point of block. In 44 patients with rheumatoid arthritis, the central nervous system showed no specific lesions at postmortem. Alterations usually attributed to aging were more pronounced, however, in the arthritics than in a control group of similar age distribution. These changes were found especially in the lateral projections of the anterior horns. Lesions were found in the peripheral nerves (in 26 out of 31 cases) and in the muscles (in 8 out of 14 cases) similar to those reported by other observers. Direct involvement of the neuromuscular system by the disease process seems highly likely in rheumatoid arthritis and may explain the neurologic signs and symptoms so prominent in this disease, including muscle weakness and atrophy. The spontaneous skeletal muscle activity in rheumatoid arthritis may also be explained on the basis of pathologic lesions of the lower motor neurones, with corroborative evidence furnished by the closely similar electromyographic pattern found in known disorders of this portion of the nervous system. (Am. J. M. Sci., July '47 - L. R. Morrison et al.)

\* \* \* \* \*

(Not Restricted)

Activation of Dental Components of the Volunteer Naval Reserve: Announcement has been made of the activation in the Third Naval District of Volunteer Dental Division 3-1, under the command of Commander Thomas Rockford, DCR, USNR, and Volunteer Dental Division 3-2, under the command of Commander Morris Orgel, DCR, USNR. Each of these divisions will have departments of operative dentistry, prosthetic dentistry, oral pathology, oral surgery and oral diagnosis with the necessary officer and enlisted personnel to man them completely.

The Eleventh Naval District has announced the activation of Volunteer Dental Division 11-1, with Captain Ivy W. Parks, DCR, USNR, in command, and Volunteer Dental Division 11-2, with Captain Perry M. Shaw, DCR, USNR, in command. (Dental Div., BuMed)

\* \* \* \* \*

(Not Restricted)

Training of Dental Technicians in Organized Surface Division: Lieutenant Wallace S. Andrews, DCR, of the Voluntary U. S. Naval Reserve, has been attached to Organized Surface Division 11-8, in the Eleventh Naval District, as Officer-in-Charge of a Reserve Dental Corps School for the purpose of training dental technicians as well as conducting routine examinations of recruits. Fifteen of the thirty billets for hospital corpsmen in this division have been reserved for dental technicians. (Dental Div., BuMed)

\* \* \* \* \*

(Not Restricted)

Training in Preventive Medicine: The Bureau of Medicine and Surgery announces the availability of courses in Preventive Medicine leading to a Master's Degree in Public Health. It is possible for the trainee to major in Public Health, Medical Statistics, Tropical Medicine, or Industrial Medicine. Courses will begin this fall at Johns Hopkins University, Harvard University, and Columbia University.

The eligibility requirements for this training have been changed in order to provide opportunities for the younger medical officers (including junior grade lieutenants) to enter this field. Reserve medical officers are eligible for consideration providing their request for training is accompanied by a request for transfer to the regular Navy. All applicants must agree not to resign during the course and to remain in the Navy for three years after completion of the course.

(Not Restricted)

Requests from medical officers should be submitted at once and in accordance with the application form contained in the Bumed News Letter dated 23 May 1947. Requests may be submitted by despatch. (Professional Div., BuMed)

\* \* \* \* \*

(Not Restricted)

Research and Special Assignments: The Bureau of Medicine and Surgery has special billets to which medical officers are assigned for research and investigation in various problems of a purely medical or medico-military nature. Assignment to these special billets is often made from medical officers who have received preliminary training in either submarine medicine or aviation medicine because the nature of the training given by the Navy in these two specialties fits them, admirably, for duty of this type, but such previous training or similar background is not necessarily required.

It is desired to bring to the attention of all medical officers, and particularly those Reserves who reported for their first active duty in July 1947, the availability of these duty assignments.

Medical officers who would like to do research or investigative work in any special field of medicine and who may or may not have experience or training in that kind of work should notify the Bureau accordingly with a note of the subjects in which they are particularly interested and the research experience they have had, if any.

It may not be possible to have all officers who apply assigned to this kind of duty, but a list will be made of those interested so that later assignment can be made as additional problems arise or other need for research develops. No service agreement is necessary. (Professional Div., BuMed)

\* \* \* \* \*

(Not Restricted)

Official Changes in BuMed Section of Catalog of Navy Material: The following items are now available for issue by Naval Medical Supply Depots:

<u>Expend- ability</u>	<u>JAN No.</u>	<u>Nomenclature and Description</u>	<u>Unit</u>	<u>Standard Unit Price</u>
X	1-225-700	Guaiac, 1 oz: NF	Btl	.30

(Newly Standardized Item).

(Not Restricted)

<u>Expend- ability</u>	<u>JAN No.</u>	<u>Nomenclature and Description</u>	<u>Unit</u>	<u>Standard Unit Price</u>
X	1-335-800	Petrolatum, 1/2 oz., 2s: USP; in tubes. (For Special Assemblies or Field Use Only).	Pkg	.10
(Newly Standardized Item).				
X	3-074-140	Stamp, Rubber Audiometer Chart Marking:	Each	.60
(Newly Standardized Item).				
	6-014-280	Dryer and Loading Bin Combination, Radiographic, Field, 110 volt, 60 cycle, AC: Approximately 790 watts. Complete with air circulator. For exhaust duct requisition 6-014-600. For special assemblies or Field use.	Each	300.00
(Newly Standardized Item).				
	6-126-050	Transformer and Control Unit, X-ray, 200 MA Capacity, 220 volt, 60 cycle, AC: Complete with shockproof, oil immersed 200 MA X-ray tube unit. For use with 6-126-010	Each	3581.00
(Newly Standardized Item).				
	7-085-302	Container, Dressing 9-1/2 inch: (Sterilizer drum). For autoclave type dress- ing sterilizers 12 inches in diameter.	Each	12.25
(Newly Standardized Item).				

(Not Restricted)

<u>Expend- ability</u>	<u>JAN No.</u>	<u>Nomenclature and Description</u>	<u>Unit</u>	<u>Standard Unit Price</u>
X	7-901-020	Slippers, Hospital, Canvas, Size 4: Extra large shoe size, 11 to 13.	Pair	.72

(Newly Standardized Item).

(MatDiv., BuMed)

\* \* \* \* \*

(Not Restricted)

Public Health Foreign Reports:

<u>Disease</u>	<u>Location</u>	<u>Date</u>	<u>No. of Cases</u>
Cholera	India, Calcutta	May 25-31, '47	186
	Indochina (French), Cambodia	May 11-20, '47	66 (54 fatal)
	Cochinchina	May 21-31, '47	118 (78 fatal)
Plague	Belgian Congo, Stanleyville Prov.	May 23-31, '47	2 (1 pneumonic)
Smallpox	China, Shanghai	May 25-31, '47	75
	Great Britain, England & Wales	June 1-7, '47	8
	Ivory Coast	May 11-20, '47	238 (29 fatal)
	Niger Territory	May 1-10, '47	168 (10 fatal)
	Rhodesia (Southern)	February '47	100
		March '47	76
	Siam (Thailand)	April 27-May 10, '47	286 (56 fatal)
Typhus Fever	Bulgaria	April 13-May 10, '47	184 (16 fatal)
	Spain	April 20-26, '47	21 (3 fatal)

(Pub. Health Reps., 4 and 11 July '47)

\* \* \* \* \*

Circular Letter 47-89

14 July 1947

(Not Restricted)

To: All Ships and Stations

Subj: Resignations of Officers of the Nurse Corps, method of submission.

This letter from the Chief of BuMed states that since the enactment of Public Law 36, 80th Congress, all resignations submitted by members of the Navy Nurse Corps shall be in accordance with Article C-7001, Chapter 7, BuPers Manual.

\* \* \* \* \*

Circular Letter 47-90

14 July 1947

(Not Restricted)

To: All Ships and Stations

Subj: Report of Dental Prosthetic Treatment, and Monthly Prosthodontia Report, Use of Standard Unit Prices for Precious Metal Expenditures Listed on.

Refs: (a) BuMed C.L. 46-79, reprinted 15 May 1946, N.D. Bulletin as Item 46-1018.  
(b) Standard Price Supplement to Class 5 BuMed Section, Catalog of Navy Material.

This letter from the Chief of BuMed directs that the dental departments of all ships and stations be precise in their use of the standard unit prices as contained in reference (b) for precious metal values reported in forms NavMed-L and NavMed-610.

\* \* \* \* \*

Circular Letter 47-91

16 July 1947

(Not Restricted)

To: ComdtsNDS, Continental United States; ComdsNavTraCens;  
ComdGensMarCorBaks, CONavTraSta NB, Newport, R. I.;  
CONavTraCen, NS, NorVa; Superintendent, NavAcad, Annapolis,  
Maryland.

Subj: Tuberculin-Testing of Navy and Marine Corps Personnel

This letter from the Chief of BuMed states that a tuberculin test shall be made of all Navy and Marine Corps personnel as soon as practicable after

(Not Restricted)

reporting to the training activities addressed. Instructions for making the test, and interpreting and recording the results in the Health Record are included. A record of all such tests shall be maintained and reported in the Quarterly Sanitary Report, giving the number tested and the reactions obtained.

\* \* \* \* \*

Circular Letter 47-92

22 July 1947

(Not Restricted)

To: All Shore Stations (except hospitals)

Subj: Dental Department - Instructions regarding Financial and Property Accountability.

Refs: (a) ALNAV 343 of 27 June 1946.  
(b) SecNav ltr Op21D-jc Serial 3369P24 A18/P5-1 dated 27 June 1946.  
(c) BuMed CirLtr 47-33 dated 17 March 1947. (ND Bulletin, 31 March 1947.)  
(d) BuMed CirLtr 45-163 dated 30 June 1945.  
(e) BuMed ltr L1-1-1948 EN dated 7 July 1947 to all shore stations.  
(f) Pars 3086, 3100 and 3101, Chapter 20, Finance and Property, Manual of the Medical Department.

Encl: 1. (HW) Instructions for reporting Dental Department receipts and expenditures on NavMed E.

This letter from the Chief of BuMed contains instructions designed to clarify references (a) and (b) in regard to the responsibility for financial and property accountability of Dental Departments and directs certain procedures that will enable the Bureau to determine the total cost for dentistry in the Navy.

\* \* \* \* \*